International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 7 Issue 2, March-April 2023 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Formulation Development and in Vitro Evaluation of Capecitabine Immediate Release Tablets

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ABSTRACT

The aim of this study is to formulate and significantly improve the bioavailability and reduce the side effects of immediate release tablets Capecitabine. The precompression blends of Capecitabine were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend of all the batches indicates good to fair flowability and compressibility. Immediate release tablets were prepared with various disintegrants like PEG 6000, Croscarmellose sodium and Sodium- starch glycolate at different concentration ratios and were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all tests. Among all the formulations F7 formulation containing, drug and Croscarmellose sodium showed good result that is 98.12 % in 45 min. Hence from the dissolution data it was evident that F7 formulation is the better formulation.

KEYWORDS: *Capecitabine, PEG 6000, Croscarmellose sodium and Sodium-starch glycolate, Immediate release*

How to cite this paper: Dr. G. Jagadish | Dr. Vibhor Kumar Jain | Rama Shukla "Formulation Development and in Vitro Evaluation of Capecitabine Immediate Release Tablets" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-7 | Issue-2, April 2023, pp.566-574, URL: www.ijtsrd.com/papers/ijtsrd55058.pdf

IJTSRD55058

INTRODUCTION:

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration . In Formulation of immediate release the commonly Superdisintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone.[1]

Oral route of administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems does not need sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. There is

requirement for new oral drug delivery system because of poor patient acceptance for invasive methods, requirement for investigation of new market for drugs and combined with high cost of disease management. Developing new drug delivery techniques and that utilizing in product development is critical for pharma companies to survive this century.[2,3, 4]

The term 'immediate release' pharmaceutical formulation is the formulation in which the rate of release of drug and/or the absorption of drug from the formulation, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage form is those which break down quickly and get dissolved to release the medicaments. In the present case, immediate release may be provided of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not delay, to an appreciable extent, the rate of drug release and/or absorption.[5,6,7]

Immediate release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main requirement for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat undesirable imperfection or disease.[8]

Pharmacokinetics:

It is the study of absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamic:

- Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.
- Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- Decreased sensitivity of the CVS to α-adrenergic agonist and antagonist.
- Immunity is less and taken into consideration while administered antibiotics.
- Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline
- shows increased sensitivity to barbiturates.
- Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.
- Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.[9]

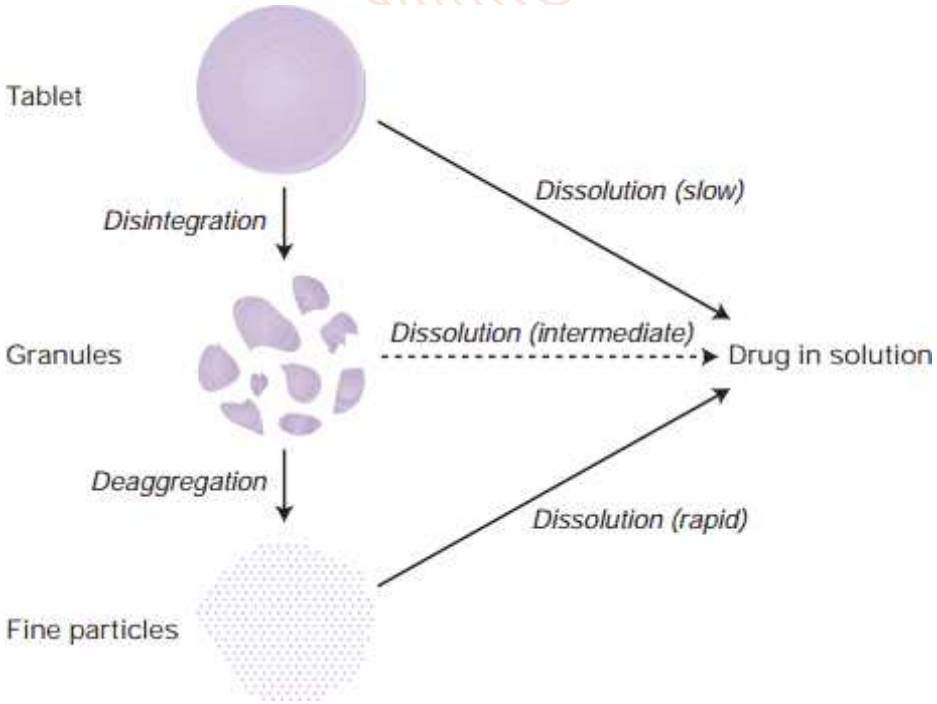

Fig 1: Drug release and dissolution process of an oral tablet

Type and Classes of Tablets :

A. Oral Tablets for Ingestion [10-11]

- Compressed tablets
- Multiple compressed tablets
- Layered tablets
- Compression-coated tablets
- Repeat-action tablets
- Delayed-action and enteric-coated tablets
- Sugar and chocolate-coated tablets
- Film coated tablets
- Chewable tablets

B. Tablets Used in the Oral Cavity[12]

- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones

C. Tablets Administered by Other Routes [10-14]

- Implantation tablets
- Vaginal tablets

D. Tablets Used to Prepare Solutions [14]

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

MATERIALS AND METHODS

Capecitabine Provided by **Aspen Pharma, Hyderabad.** PEG 6000 from Nihar traders' pvt Ltd. Croscarmellose sodium from Nihar traders pvt Ltd. Sodium-starch glycolate from Nihar traders pvt Ltd. Mannitol from Nihar traders pvt Ltd. MCC from Himedia Laboratories. Magnesium stearate from Nice chemicals Ltd. Talc from Nihar traders pvt Ltd.

Analytical method development for Capecitabine:

Formulation Development:

- Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table 1: Formulation of Immediate Release tablets

INGREDIENTS	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Capecitabine	200	200	200	200	200	200	200	200	200	200	200	200
PEG 6000	30	60	90	120	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	30	60	90	120	-	-	-	-
Sodium-starch glycolate	-	-	-	-	-	-	-	-	30	60	90	120
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total weight	400	400	400	400	400	400	400	400	400	400	400	400

Total weight of tablets = 400 mg

RESULTS AND DISCUSSION

Determination of λ max:

The Prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 280 nm.

Calibration curve of Capecitabine:

The standard curve of Capecitabine was obtained and good correlation was obtained with R^2 value of 0.999 the medium selected was pH 6.8 phosphate buffer.

Table 2: Standard graph values of Capecitabine at 280 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.126
10	0.241
15	0.352
20	0.461
25	0.581

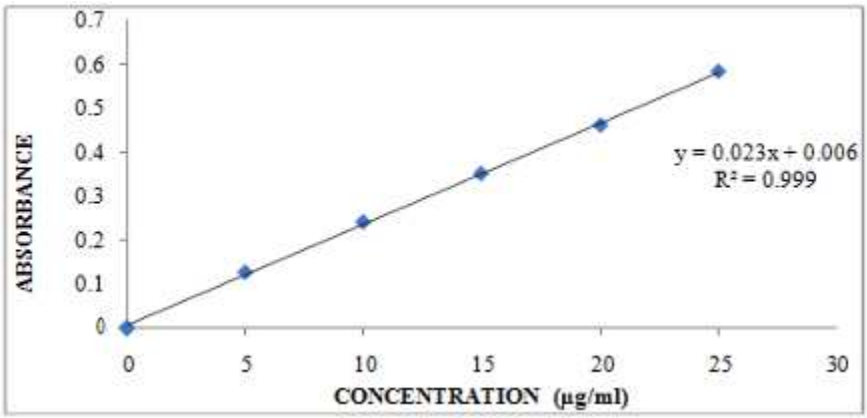

Fig 2: Standard curve of Capecitabine

Evaluation:

Characterization of precompression blend:

The precompression blend of Capecitabine was characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 34.0 ± 0.05˚, Carr's index values were less than 22.5 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than for all batches indicating good flow properties.

Table 3: Physical properties of precompression blend

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	40.4 ± 0.03	0.50 ± 0.09	0.62 ± 0.02	21.3 ± 0.07	1.26 ± 0.07
F2	34.0 ± 0.05	0.51 ± 0.08	0.64 ± 0.03	21.4 ± 0.14	1.23 ± 0.06
F3	29.5 ± 0.11	0.47 ± 0.11	0.56 ± 0.05	16.4 ± 0.13	1.15 ± 0.13
F4	31.8 ± 0.03	0.52 ± 0.08	0.64 ± 0.04	22.5 ± 0.09	1.27 ± 0.10
F5	37.7 ± 0.12	0.51 ± 0.10	0.62 ± 0.06	19.5 ± 0.06	1.23 ± 0.15
F6	36.2 ± 0.13	0.50 ± 0.07	0.62 ± 0.03	19.8 ± 0.06	1.24 ± 0.14
F7	40.1 ± 0.12	0.54 ± 0.09	0.65 ± 0.06	21.4 ± 0.06	1.26 ± 0.13
F8	33.4 ± 0.07	0.51 ± 0.05	0.63 ± 0.06	20.4 ± 0.12	1.23 ± 0.07
F9	26.2 ± 0.12	0.48 ± 0.04	0.57 ± 0.03	17.4 ± 0.07	1.15 ± 0.04
F10	31.4 ± 0.08	0.52 ± 0.06	0.64 ± 0.07	21.5 ± 0.03	1.23 ± 0.07
F11	29.6 ± 0.17	0.50 ± 0.02	0.62 ± 0.04	18.3 ± 0.04	1.20 ± 0.12
F12	30.3 ± 0.09	0.51 ± 0.06	0.64 ± 0.03	20.1 ± 0.08	1.23 ± 0.10

All the values represent n=3

Evaluation of tablets:

Physical evaluation of Capecitabine Immediate release tablets: The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 8.3. All the tablets of different batches complied

with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 4.11-4.61 kg/cm^2 and the friability values were 0.12 – 0.64 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.11 – 3.61 cm. All the formulations satisfied the content of the drug as they contained 97.15- 99.75 % of Capecitabine and good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Table 4: Physical evaluation of Capecitabine

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	398.2	4.14	5.5	0.12	98.26
F2	399.4	4.52	5.1	0.29	97.15
F3	396.8	4.61	5.9	0.61	99.62
F4	395.2	4.42	5.4	0.24	98.35
F5	398.8	4.11	5.6	0.56	99.29
F6	397.1	4.28	5.1	0.35	98.61
F7	399.8	4.42	5.5	0.48	99.75
F8	397.5	4.51	5.6	0.64	97.82
F9	398.6	4.29	5.4	0.53	99.12
F10	399.0	4.18	5.2	0.42	97.49
F11	398.7	4.38	5.5	0.52	99.31
F12	398.9	4.16	5.7	0.39	97.86

***In vitro* release studies:**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 280 nm.

Table 5: *In vitro* data for formulation F1-F4

TIME (MIN)	% DRUG RELEASE			
	F1	F2	F3	F4
0	0	0	0	0
5	19.32	22.15	34.91	28.62
10	25.39	32.47	41.82	36.56
15	46.75	45.32	56.94	45.84
20	67.28	63.79	68.66	59.42
25	73.41	78.34	82.24	78.82
30	79.63	82.47	87.11	89.94
45	83.82	89.68	93.23	96.44

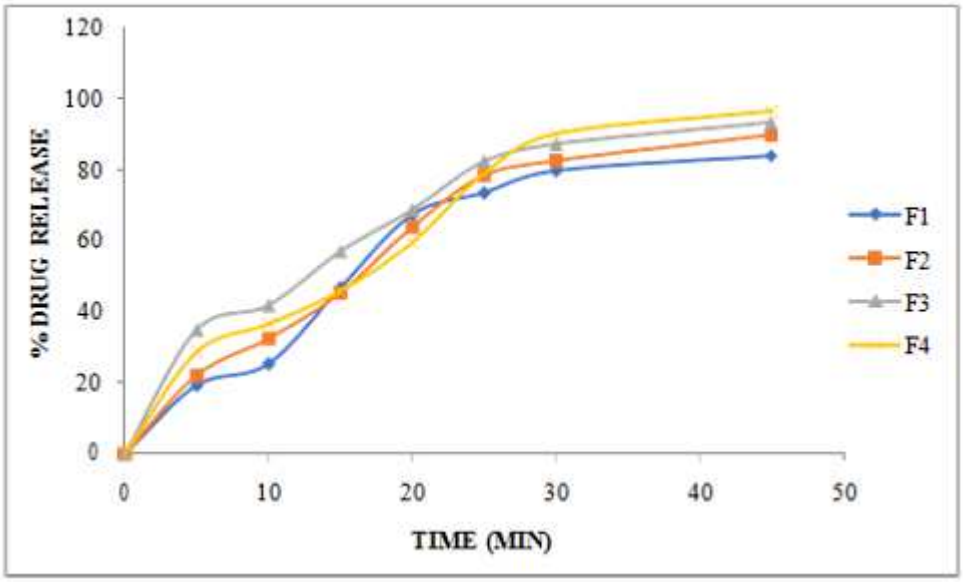

Fig 3 : *In vitro* dissolution data for formulation F1-F4

Table 6: *In vitro* dissolution data for formulations F5-F8

TIME(MIN)	% DRUG RELEASE			
	F5	F6	F7	F8
0	0	0	0	0
5	23.62	32.91	30.52	25.47
10	35.11	41.63	43.33	36.94
15	47.25	54.28	53.75	44.79
20	59.41	65.15	75.85	65.57
25	67.37	68.82	82.54	72.64
30	73.85	73.65	88.76	84.84
45	76.65	84.56	98.12	91.32

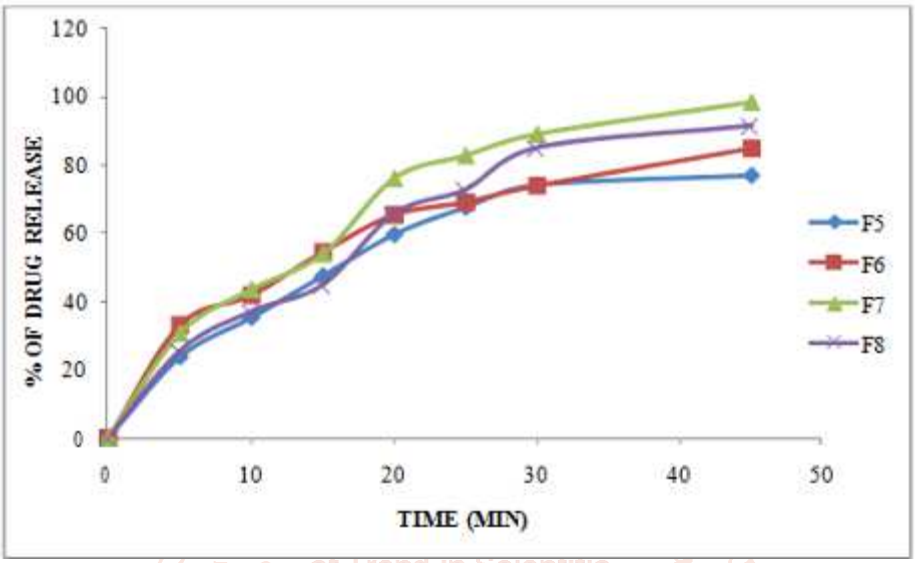

Fig 4: *In vitro* dissolution data for formulations F5-F8

Table 7: *In vitro* dissolution data for formulations F9-F12

TIME (MIN)	% DRUG RELEASE			
	F9	F10	F11	F12
0	0	0	0	0
5	25.91	21.62	18.85	15.59
10	37.15	29.10	29.68	34.41
15	45.20	45.81	38.92	38.98
20	57.38	58.99	46.58	49.12
25	79.82	67.38	58.28	58.78
30	86.73	74.87	65.96	63.93
45	95.19	86.56	72.48	68.56

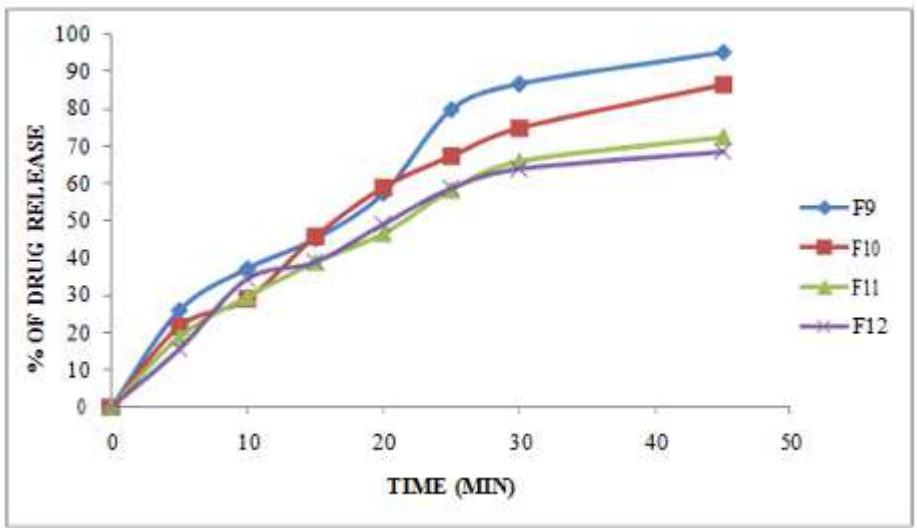

Fig 5: *In vitro* dissolution data for formulations F9-F12

Among all the formulations F7 formulation containing drug and Croscarmellose sodium showed good result that is 98.12 % in 45 minutes, at the concentration of 90 mg. Hence from all the formulations it is evident that F7 formulation is the better formulation.

Drug-Excipient compatibility studies by FTIR studies:

Capecitabine was mixed with various proportions of excipients showed no colour change at the end of two months, providing no drug –excipient interactions.

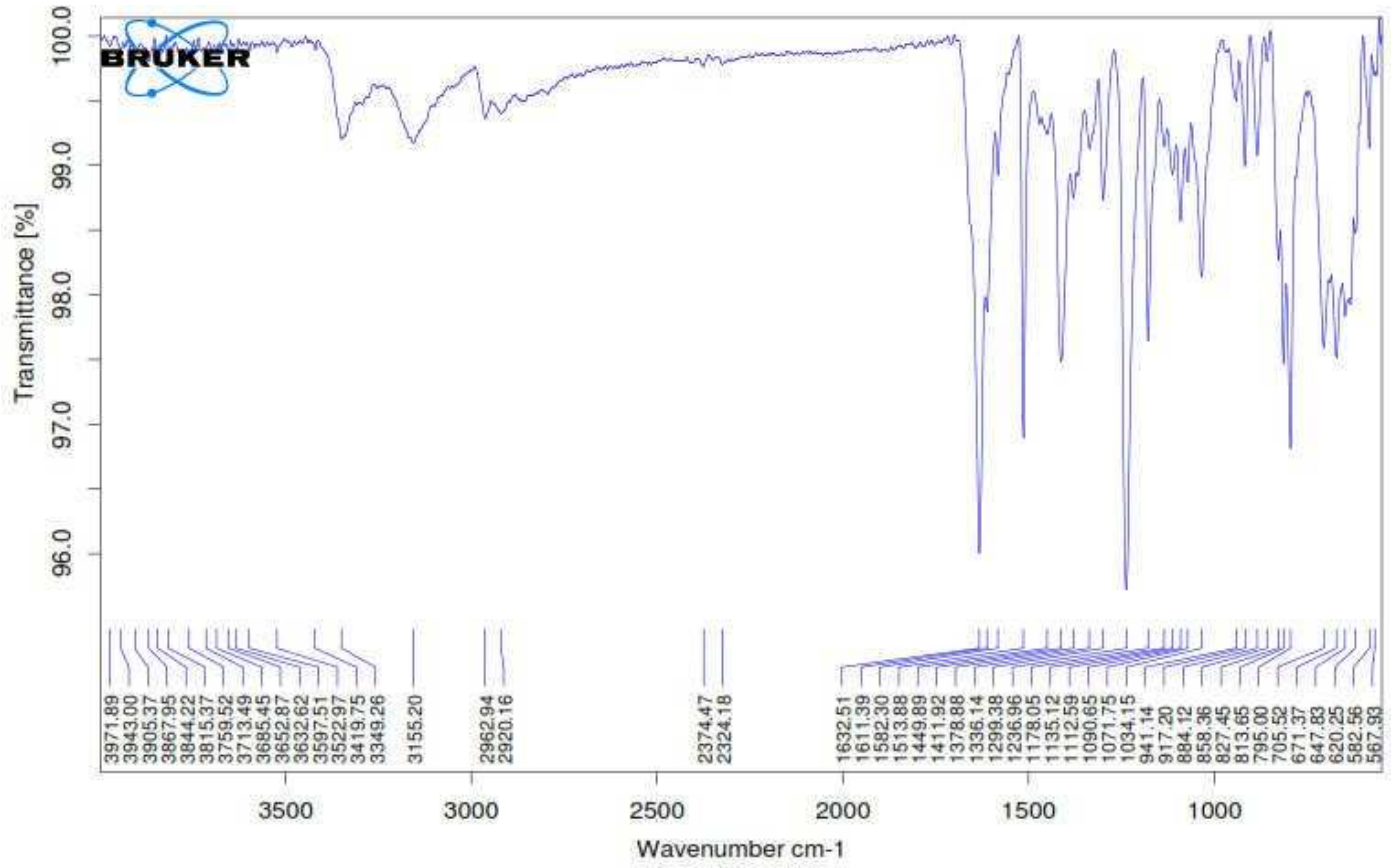

Fig 6: FTIR spectra of pure drug

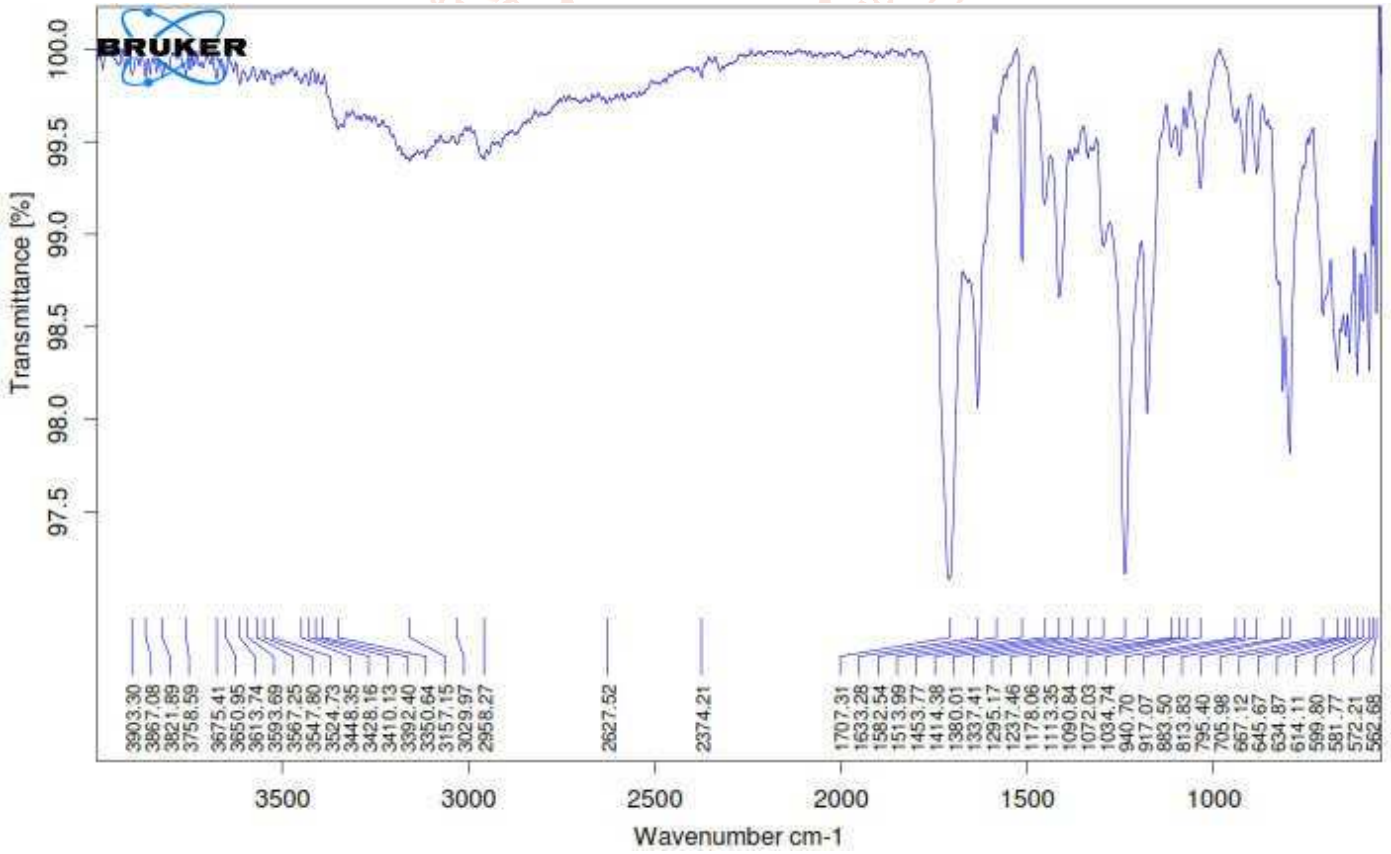

Fig 7: FTIR spectra of optimized formulation

CONCLUSON

- The standard curve of Capecitabine was obtained and good correlation was obtained with R^2 value of 0.999. The medium selected was pH 6.8 phosphate buffer.
- Capecitabine was mixed with various proportions of excipients showed no colour change at the end of 2 months, proving no drug-excipient interactions.
- The precompression blend of Capecitabine immediate release tablets using super disintegrants were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend or all batches indicating good to fair flowability and compressibility.
- Immediate release tablets were prepared with various concentrations of disintegrants and were compressed into tablets.
- The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests.
- The formulations (F7) prepared with Croscarmellose sodium disintegrant showed drug release in increasing order. The formulation (F7) containing drug and Croscarmellose sodium showed good drug release at 90 mg concentration.
- Among all the formulations F7 formulation containing drug and Croscarmellose sodium (90 mg concentration) showed maximum and good result that is 98.12% drug release in 45 min. Hence from dissolution data it was evident that F7 formulation is the better formulation.

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